



**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**  
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>SCB 789 PCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/EP 03/05893</b>	International filing date ( <i>day/month/year</i> ) <b>05.06.2003</b>	Priority date ( <i>day/month/year</i> ) <b>07.06.2002</b>
International Patent Classification (IPC) or both national classification and IPC <b>A61K31/47</b>		
Applicant <b>MENARINI RICERCHE S.P.A. et al.</b>		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"><li>I <input checked="" type="checkbox"/> Basis of the opinion</li><li>II <input type="checkbox"/> Priority</li><li>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li><li>IV <input type="checkbox"/> Lack of unity of invention</li><li>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li><li>VI <input type="checkbox"/> Certain documents cited</li><li>VII <input type="checkbox"/> Certain defects in the international application</li><li>VIII <input type="checkbox"/> Certain observations on the international application</li></ul>		
Date of submission of the demand  <b>10.12.2003</b>	Date of completion of this report  <b>10.09.2004</b>	
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized Officer  <b>Bérillon, L</b>  Telephone No. <b>+49 89 2399-7078</b>  	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP 03/05893

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-55 as originally filed

**Claims, Numbers**

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-13
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-13
Industrial applicability (IA)	Yes: Claims	1-13
	No: Claims	

2. Citations and explanations

**see separate sheet**

**Item V**

**1 Prior art**

Reference is made to the following documents:

D1: US-A-5968951  
D2: US-A-6063791  
D3: US-B1-6211196  
D4: US-A-5859025  
D5: US-A-6140341

**2 Novelty (Article 33(2) PCT)**

- 2.1 The present compounds are novel over D2-D4 in view of their  $\alpha,\alpha$  disubstituted amino acid group.
- 2.2 The present compounds overlap with those disclosed in D1 (see e.g. formula (I) with A is a branched alkylene chain, B is a single bond,  $R_3$  is  $COR_6$  and  $R_6$  is  $NR_4 R_5$ ). However, the subject matter of the overlapping area relates to a new technical teaching: the presence of a  $\alpha,\alpha$  disubstituted amino acid group and can therefore be regarded as a novel selection.

Accordingly, novelty is acknowledged for the present application.

**3 Inventive step (Article 33(3) PCT)**

- 3.1 D1 which represents the closest prior art discloses compounds which are bradykinin antagonists useful as anti-inflammatory agents, analgesics etc.  
The technical problem underlying the present application is regarded as the provision of further bradykinin antagonists. Said problem has been solved with present compounds of formula (I) as shown by the biological tests on page 55. However, the present compounds cannot be considered as an inventive solution to the above mentioned technical problem since they just represent a selection of the compounds disclosed in D1 (see item 2.2). The skilled person aware of D1 and seeking further bradykinin antagonists would have therefore considered the present compounds

without the exercise of inventive step.

It should in addition be noted that documents D2-D5 disclose compounds which are bradykinin antagonists and which equally present structural variation at the same position of the quinolin-8-yloxymethylphenyl ring. D4 and D5 even disclose bradykinin antagonists which do not have the sulfonamide linker but instead a substituted amino and an alkoxy substituent respectively. The skilled person would therefore expect said antagonistic activity to be present in the case of the present compounds having said  $\alpha,\alpha$  disubstituted amino acid group.

Inventive step could be acknowledged if the present compounds were shown to exhibit unexpected properties over the closest prior art (i.e. to solve unexpectedly a problem not yet solved). Comparative tests envisaged to support inventive step must be carried out between the compounds of the present application and those of the closest prior art having the maximum structural similarity (see D1, table I, e.g. compound 19) such that the effect is shown to have its origins in the distinguishing feature of the claimed invention i.e. the presence of a  $\alpha,\alpha$  disubstituted amino acid group. The comparative tests which have been provided do not meet these requirements.

- 3.2 Regarding the intermediates claimed in claims 8 and 9, it appears that they equally have the  $\alpha,\alpha$  disubstituted amino acid group which differentiate the subsequent products (i.e compound of formula (I), claim 1) from the prior art. Accordingly, they could be considered inventive in case the compounds of formula (I) are (see item 3.1).